DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

November 7, 2014

Nanostring Technologies, Inc.
Sylva Krizan, Ph.D.
Regulatory Affairs Manager
530 Fairview Avenue North, Suite 2000
Seattle, Washington 98109

Re: K141771
Trade/Device Name: Prosigna™ Breast Cancer Prognostic Gene Signature Assay
Regulation Number: 21 CFR §866.6040
Regulation Name: Gene expression profiling test system for breast cancer prognosis
Regulatory Class: Class II
Product Code: NYI
Dated: September 5, 2014
Received: September 8, 2014

Dear Dr. Krizan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of *In Vitro* Diagnostics and
Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K141771

Device Name
Prosigna® Breast Cancer Prognostic Gene Signature Assay

Indications for Use *(Describe)*

The Prosigna™ Breast Cancer Prognostic Gene Signature Assay is an in vitro diagnostic assay which is performed on the NanoString nCounter® Dx Analysis System using FFPE breast tumor tissue previously diagnosed as invasive breast carcinoma. This qualitative assay utilizes gene expression data, weighted together with clinical variables to generate a risk category and numerical score, to assess a patient's risk of distant recurrence of disease.

The Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as:

1. A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-negative, Stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.

2. A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-positive (1-3 positive nodes), Stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The device is not intended for patients with 4 or more positive nodes.

Special Conditions for Use: Prosigna is not intended for diagnosis, to predict or detect response to therapy, or to help select the optimal therapy for patients.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Yun-fu Hu -S

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510(k) Summary K141771

Applicant:
NanoString Technologies, Inc.

Establishment Registration Number:
3006389928

Contact person:
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Summary Date:
November 7, 2014

Device Name:
Trade name: Prosigna® Breast Cancer Prognostic Gene Signature Assay
Common Name: NanoString gene expression profiling test for breast cancer prognosis

Classification:
21 CFR § 866.6040: Gene expression profiling test system for breast cancer prognosis

Guidance Document:
Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis, issued on May 9, 2007

Product Code:
NYI

Indications for Use / Intended Use:

The Prosigna® Breast Cancer Prognostic Gene Signature Assay is an in vitro diagnostic assay which is performed on the NanoString nCounter® Dx Analysis System using FFPE breast tumor tissue previously diagnosed as invasive breast carcinoma. This qualitative assay utilizes gene expression data, weighted together with clinical variables to generate a risk category and numerical score, to assess a patient's risk of distant recurrence of disease.

The Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as:

1. A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-negative, Stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.

2. A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-positive (1-3 positive nodes), Stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The device is not intended for patients with 4 or more positive nodes.

Special Conditions for Use:
Prosigna is not intended for diagnosis, to predict or detect response to therapy, or to help select the optimal therapy for patients.

Device Description:

Used together, the Prosigna® Breast Cancer Prognostic Gene Signature Assay and nCounter Dx Analysis System are a nucleic acid hybridization, visualization and image analysis system based upon coded probes designed to detect the messenger RNA transcribed from 58 genes. The test input is purified RNA from FFPE breast tumor specimens which are acquired from surgical resection. The Prosigna assay uses gene-specific probe pairs that hybridize directly to the mRNA transcripts in solution. The nCounter Dx Analysis System delivers direct, multiplexed measurements of gene expression through digital readouts of the relative abundance of the mRNA transcripts. Specifications are included as part of the Prosigna Assay to control for sample quality, RNA quality, and process quality. Prosigna simultaneously measures the expression levels of 50 genes used in the PAM50 classification algorithm (Parker et al., 2009), 8 housekeeping genes used for signal normalization, 6 positive controls, and 8 negative controls in a single hybridization reaction, using nucleic acid probes designed specifically to those genes. The Prosigna assay utilizes prototypical expression profiles (centroids) which are associated with and define each of the four PAM50 molecular subtypes of breast cancer. The software algorithm produces a Prosigna Score (referred to as ROR Score or Risk of Recurrence Score in the literature (Dowsett et al., 2013)) based on the similarity of the expression profile to each PAM50 molecular subtype, as well as the gross pathological tumor size and a proliferation score computed from a subset of genes. Three risk categories (Low, Intermediate and High) were defined based on a study with over 1007 patient samples associating Prosigna score with long-term outcome.

The required components for the Prosigna Assay include the RNA Isolation kit (manufactured by Roche), Prosigna reagents (Reference Sample, CodeSet, Prep Pack, Cartridge(s) and Prep Plate) and the instruments that comprise the nCounter Dx Analysis System; the Prep Station and Digital Analyzer.

The test output is a patient specific report which includes a Prosigna Score (0-100) and risk category (low/intermediate/high) where indicated.

Analytical Performance:

A number of pre-analytical and analytical studies were carried out with the Prosigna Assay to assess the precision, reproducibility, cutoff, sensitivity, specificity and robustness of the assay. Analytical studies also addressed specimen shipping and storage, reagent stability, RNA extraction specifications, tissue requirements, RNA input, cross-hybridization, cross-contamination and tissue interferents testing.

Technical validity was demonstrated in two multi-site (3 sites total), blinded and randomized studies which were designed to test variability across operators, sites, instruments, reagent lots, time, runs and sample position within a 10-sample cartridge. One study assessed reproducibility including pre-analytical factors with a total of 43 tissue samples (FFPE) and the other assessed assay precision with 5 pooled RNA samples. All reproducibility samples were within the intended use patient population indicated by Prosigna, and constituted a large range of Prosigna scores (across 94 Prosigna Score units).

The standard deviation (SD) of the Prosigna score from the 5 pooled RNA samples was < 1 Prosigna Score unit across 3 sites, 3 reagent lots, and 108 measurements of each RNA sample. Using a linear regression and correlation analysis, the normalized gene expression from the 50 classifier genes was compared between the replicate tumor RNA hybridization measurements from all valid samples tested at each site. The average intercept, slope, and Pearson's correlation (r) of the pair-wise comparisons are reported with the 95 % confidence interval. At each site, the normalized gene expression between RNA replicates was highly correlative with slopes ranging from 0.98 – 1.00, intercepts at 0, and r values of 0.99.

Pairwise correlation for Replicate RNA Hybridizations from tissue reproducibility study

Pairwise Comparison of Replicate RNA Hybridizations				
Comparison	**Pairwise Comparisons (n)**	**Intercept [95% CI]**	**Slope [95% CI]**	**r [95% CI]**
All Sites	124	0.00 [-0.01 , 0]	0.99 [0.99 , 1]	0.99 [0.99 , 0.99]
Site 1	40	-0.01 [-0.01 , 0]	1.00 [0.99 , 1.01]	0.99 [0.99 , 0.99]
Site 2	41	0.00 [-0.01 , 0.01]	0.98 [0.97 , 0.99]	0.99 [0.99 , 0.99]
Site 3	43	0.00 [-0.01 , 0.01]	0.99 [0.99 , 1]	0.99 [0.99 , 0.99]

Using a linear regression and correlation analysis, the normalized gene expression from the 50 classifier genes was also compared between the tissue replicates from all valid specimens tested at each site. The average intercept, slope, and Pearson's correlation (r) of the pair-wise comparisons between sites are reported with the 95 % confidence interval. The gene expression

between tissue replicates was highly correlative between sites with slopes ranging from 0.97 – 1.00, intercepts at 0, and r values of 0.98 or greater.

Pairwise correlation for Replicate Tissues from tissue reproducibility study

Pairwise Comparison of Tissue Replicates				
Comparison	**Pairwise Comparisons (n)**	**Intercept [95% CI]**	**Slope [95% CI]**	**r [95% CI]**
All Sites	121	0.00 [-0.01 , 0.01]	0.98 [0.97 , 0.99]	0.98 [0.98 , 0.98]
Site 1 vs. Site 2	40	0.00 [-0.01 , 0.01]	0.97 [0.95 , 0.98]	0.98 [0.97 , 0.98]
Site 1 vs. Site 3	40	0.01 [0 , 0.02]	1.00 [0.98 , 1.01]	0.98 [0.98 , 0.99]
Site 2 vs. Site 3	41	-0.01 [-0.02 , 0]	0.99 [0.97 , 1]	0.99 [0.98 , 0.99]

The total variability using the sum of the tissue processing variability (including across sites and within tissue samples) as well as the total RNA Processing Variability from the RNA precision study (averaged across the five tested RNA samples) is summarized as a total standard deviation for tissue and RNA Processing of 2.9 Prosigna Score units. A standard deviation of 2.9 Prosigna Score units demonstrates that the Prosigna Assay can reliably measure a difference between two Prosigna Scores of 6.75 with 95% confidence.

Additionally, the concordance in categorical risk classifications across the 43 tissue samples in the Tissue Reproducibility study (node-negative and positive risk categories) between all sites was very high (average concordance greater than 90%).

Additional analyses of the gene expression from samples used in the validation studies shows that the gene expression inherent to the intrinsic biology of breast cancer is the primary factor in explaining the differences in expression in this patient population, which is independent of the patient's node status. For further details, see Package Insert.

Clinical Performance:

Prosigna's clinical performance has been verified and validated in two large studies using retrospective tissue samples from 2485 patients within the Intended Use patient population. The first study, TransATAC, demonstrated that Prosigna Score was continuously related to Distant Recurrence-Free Survival (DRFS) at 10 years and was used to select the Prosigna Score cut-offs for Low, Intermediate, and High risk categories. The second study, ABCSG-8 replicated the result that Prosigna Score was continuously related to DRFS at 10 years and validated the risk group cut-offs.

Both the TransATAC and ABCSG-8 study samples were independent from those samples used to train the Prosigna algorithm.

For the ABCSG-8 study, all samples were sent to, and all tests were performed at, an independent academic pathology laboratory. Of the 1,620 tissues available for testing in the ABCSG-8 study, 25 (1.5%) did not pass pre-defined pathology review criteria for adequate tumor, 73 of the 1595 tissue samples (4.6%) with viable invasive tissue did not pass pre-defined QC specifications for quantity and quality of extracted RNA, and 44 of the 1522 RNA samples (2.9%) failed the Prosigna assay QC specifications leaving a total of 1,478 (91.2%) available for analysis. Of the 1,478 patients available for analysis, 155 had distant recurrences and 194 had local or distant recurrence or death due to breast cancer. The median follow-up for the trial was 10 years.

The table below shows a summary of the primary analysis of the ABCSG-8 study using a Cox proportional hazards model in which (1) Prosigna Score was added to the clinical treatment score (CTS) as a continuous variable and (2) Prosigna Score was added to CTS using the pre-defined Prosigna Score-based risk groups. In both cases, a null model consisting of CTS alone was compared to an alternate model using a likelihood ratio (LR) test. The table shows the test statistic ($\Delta LR\ \chi 2 = -2\ln(LR)$), the critical value for the degrees of freedom for the $\alpha = 0.05$ test, and the p-value based on the $\chi 2$ distribution.

Summary of Primary Analysis Testing from ABCSG-8 clinical validation study

Null Model	**Alternate Model**	**ΔLR χ^{2*}**	**χ^2 Critical Value (Degrees of freedom)**	**χ^2 p-value**
CTS	CTS + Prosigna Score	53.49	3.84 (df = 1)	$p < 0.0001$
CTS	CTS + Risk Groups	34.12	5.99 (df = 2)	$p < 0.0001$

*ΔLR is used to denote twice the difference of the log likelihoods when comparing two models, e.g., CTS and CTS + Prosigna Score. The statistic has an approximate χ^2 distribution.

CTS is an optimized combination of clinical and treatment variables (patient age, tumor grade, gross pathological tumor size, nodal status, and adjuvant therapy) which is a best-case approximation of how a physician may use these factors in treatment decisions. When adding Prosigna Score either as a continuous variable or using risk-groups, the Prosigna Score was shown to add significant prognostic information ($p < 0.0001$) for DRFS over and above that contained in the CTS score.

The table below shows the results of Cox modeling when CTS and the two or three Prosigna Score-based risk groups were included as covariates in the ABCSG-8 study, by nodal status.

Cox Regression Results for Pre-Defined Risk Groups in ABCSG-8 Clinical Validation Study

Node Group*	Variable	Coefficient	P-value	Hazard Ratio		
				Point Estimate	Lower 95% CL	Upper 95% CL
N0	CTS	0.70	0.0013	2.01	1.31	3.08
	Intermediate vs. Low Prosigna Score	0.96	0.0015	2.60	1.44	4.70
	High vs. Low Prosigna score	1.38	<0.0001	3.96	2.18	7.20
N1	CTS	0.69	0.0098	1.99	1.18	3.34
	High vs. Low Prosigna Score	1.44	0.0002	4.22	1.98	9.00

*N0: Node-negative, N1: Node-positive (1-3 nodes)

In the node-negative population, the hazard ratio for Intermediate vs. Low Prosigna Score is statistically significantly greater than 1 (95% confidence interval does not include 1) and that for High vs. Low Prosigna Score is statistically significantly greater than 2 (95% confidence interval does not include 2), i.e. the pre-defined Prosigna Score cutoffs separate the patients into three risk groups (Low risk, Intermediate risk, High risk) with statistically significantly different outcomes at 10 years.

In the node-positive population (1-3 nodes), the hazard ratio for High vs. Low Prosigna Score is statistically significantly greater than 2 (95% confidence interval does not include 2), i.e. the pre-defined Prosigna Score cutoffs separate the patients into two risk groups (Low risk, High risk) with statistically significantly different outcomes at 10 years.

The cutoffs for the risk group classifications were defined based on the results of the TransATAC study:

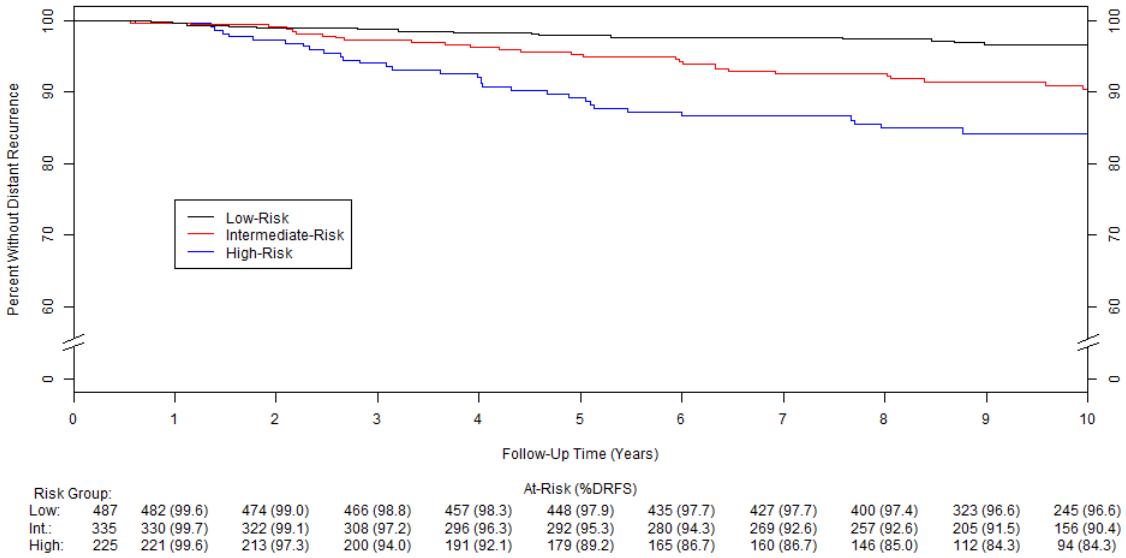
Risk Group	Risk of distant recurrence by 10 years	Prosigna Score Range for Node-Negative	Prosigna Score Range for Node-Positive (1-3 Nodes)
Low	< 10%	0-40	0-40
Intermediate	10 - 20%	41-60	
High	> 20%	61-100	41-100

The following figures are the Kaplan-Meier curves showing the percent of patients without distant recurrence by risk-group through 10 years for all patients from the ABCSG-8 study, by nodal status.

The figure below shows the Kaplan-Meier plots by risk-group for Node-Negative patients. The x-axis shows the number of patients and the percent without a distant recurrence (DR) event for each risk group. The observed incidence of distant recurrence in the Low risk node-negative patients remains consistently low over the 10 year evaluation period. Similar DR rates for these patients were observed between the first 5 years, while patients were receiving endocrine therapy, and years 5 and 10 after diagnosis, following completion of endocrine therapy. A total of 2.1% of Low risk node-negative subjects had a DR event through 5 years after diagnosis and 1.3% of subjects had a DR event between years 5 and 10 after diagnosis (3.4% total 10-year risk

of recurrence). The incidence of distant recurrence in the Intermediate risk node-negative patients also appeared similar between the first 5 years and 5 and 10 years after diagnosis, though at a consistently higher rate than the Low risk population. A total of 4.7% of these subjects had a DR event through 5 years and 4.9% of subjects had a DR event between years 5 and 10 after diagnosis (9.6% total 10-year risk of recurrence). The incidence of distant recurrence in the High risk node-negative patients appears more variable over the 10 year evaluation period. It was observed that 10.8% of these subjects had a DR event through 5 years after diagnosis and 4.9% of subjects had a DR event between years 5 and 10 after diagnosis (15.7% total 10-year risk of recurrence).

DRFS by Risk Group for Node-Negative Patients

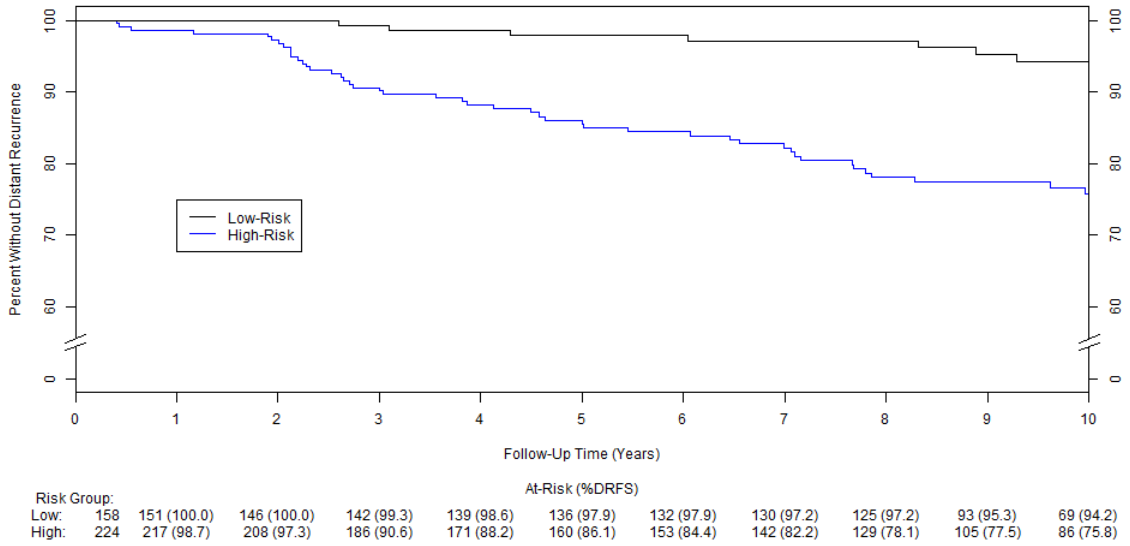


Summary: DRFS by Risk Group for Node-Negative Patients

Risk Group	Number of Patients (%)	Number of Events Through 10 Years	Estimated Percent Without Recurrence at 10 years [95% CI]
Low	487 (47%)	15	96.6% [94.4% - 97.9%]
Intermediate	335 (32%)	28	90.4% [86.3% - 93.3%]
High	225 (21%)	32	84.3% [78.4% - 88.6%]
Total	1,047 (100%)	75	

The figure below shows the Kaplan-Meier plots by risk-group for Node-Positive (1–3 nodes) patients. The x-axis shows the number of patients and the percent without a DR event for each risk group. The incidence of distant recurrence in node-positive (1-3 nodes) patients remains consistently lower in the Low Risk group than in the High risk group. In the Low risk group, 2.1% of patients had a DR through 5 years after diagnosis and 3.7% had a distant recurrence event between years 5 and 10 after diagnosis (5.8% total 10 year risk of recurrence). In the High risk Node-Positive (1–3 nodes) patients the incidence of distant recurrence is 13.9% during the initial 5 years of endocrine therapy and 10.3% between years 5 and 10 after diagnosis (24.2% total 10-year risk of recurrence).

DRFS by Risk Group for Node-Positive (1-3 nodes) Patients



Summary: DRFS by Risk Group for Node-Positive (1-3 nodes) Patients

Risk Group	Number of Patients (%)	Number of Events Through 10 Years	Estimated Percent Without Distant Recurrence at 10 years [95% CI]
Low	158 (41%)	7	94.2% [88.1%-97.2%]
High	224 (59%)	46	75.8% [68.9%-81.4%]
Total	382 (100%)	53	

The Prosigna Score was demonstrated to add significant prognostic information over and above the standard clinical and treatment variables both when included as a continuous measure and when included using pre-defined risk groups. The low-risk groups (each of node-negative and node-positive patients) had 10-year DRFS well above 90% and was separated from the high-risk group by more than a 10% probability of recurrence at 10 years. The Prosigna Score (continuous and risk-group based) showed similar prognostic information in various subgroups.

A C-index analysis was used to evaluate the correlation between the Prosigna Score and the time to distant recurrence. The C-index analysis was restricted to comparing patient samples with Prosigna Scores that differed by only 5-10 Prosigna Score units. This analysis showed that there is statistically significant information in small changes in Prosigna Score ($P<0.05$). Based on the analytical precision and reproducibility studies and the restricted C-index analysis of 5-10 ΔProsigna Score units, a difference of Prosigna Score of 7 is shown to be both a reliable measure of difference of the Prosigna test performance (statistically reproducible based on analytical studies), and of clinical utility (clinically meaningful based on restricted C-index analysis).

For both node-negative and node-positive (1-3 nodes) patients, the event rates within some risk groups were not constant across the 10-year interval (see figures above). Based upon post-hoc analysis of the 10 year data, for High risk patients more DR events appeared to occur in the first 5 years of the overall 10-year risk period, while Intermediate and Low risk patients showed similar rates of DR in between the first 5 years and years 5 to 10 of the ABCSG-8 study. The Prosigna Score provided insight into the probability of DR events in the first 5 years, while patients were receiving endocrine therapy, and years 5 and 10 after diagnosis, following completion of endocrine therapy.

The behavior of the risk-groups is no different across all patients when the population is restricted to Her2-negative patients.

The analytical performance studies in combination with pre-analytical studies validate that the Prosigna assay is appropriate for use as a distributed gene expression profiling test system for breast cancer prognosis. The clinical studies demonstrate the validity of a risk classifier that includes High, Intermediate and Low risk groups (where indicated) as well as a continuous risk score that outputs an integer Prosigna Score of 0-100.

Predicate Device:
Prosigna Breast Cancer Prognostic Gene Signature Assay K130010

Substantial Equivalence Comparison Table		
Device	Predicate Device: Prosigna Breast Cancer Prognostic Gene Signature Assay, K130010	Modified Device: Prosigna® Breast Cancer Prognostic Gene Signature Assay, K141771
Intended Use	The Prosigna® Breast Cancer Prognostic Gene Signature Assay is an in vitro diagnostic assay which is performed on the NanoString nCounter® Dx Analysis System using FFPE breast tumor tissue previously diagnosed as invasive breast carcinoma. This qualitative assay utilizes gene expression data, weighted together with clinical variables to	Same as marketed device

	generate a risk category and numerical score, to assess a patient's risk of distant recurrence of disease. The Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as: 1. A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-negative, Stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. 2. A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-positive (1-3 positive nodes), Stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The device is not intended for patients with 4 or more positive nodes.	
Indications	Same as intended use	Same as intended use
Special conditions for use statement(s)	For prescription use only. Prosigna® is not intended for diagnosis, to predict or detect response to therapy, or to help select the optimal therapy for patients	Same as marketed device
Device Description	Prosigna® Breast Cancer Prognostic Gene Signature Assay and nCounter Dx Analysis	Same as marketed device

	Platform; all elements cleared by FDA as a distributed test and platform	
Test Sample	FFPE tumor samples	Same as marketed device
Extraction/amplification reagents/amplification procedures	No amplification required; procedure for processing FFPE tumor samples provided; includes RNA isolation, multiplex hybridization in solution, automated purification on a liquid handling robot and analysis on an automated epifluorescence microscope	Same as marketed device
Validation population	Treatment arms from a randomized trial conducted in Europe; prospective retrospective study design	Same as marketed device
Method Comparison Results	Not applicable	Deming Regression and Bland-Altman Analysis demonstrate that software changes (including Dual Use FLEX configuration) and addition of 4-test configuration are equivalent to K130010
Clinical Studies	1478 patients evaluated resulting in overall percentage without distant recurrence at 10 years separated by three risk groups in node-negative patients (n=1047): Low risk 96.6% (94.4%-97.9%), Intermediate risk 90.4% (86.3%-93.3%), High risk 84.3% (78.4%-88.6%) and by two risk groups in node-positive (1-3 nodes) patients (n=382): Low risk 94.2% (88.1%-97.2%), High risk 75.8% (68.9%-81.4%)	Same as marketed device
Kit Stability/ Shelf Life	7 months, based on testing completed at time of clearance	8 months, based upon real time stability data available from original testing protocol
Device Configuration	Reagents configured and software programmed to prepare samples in 2 control wells and 10 sample wells-10 test configuration	Reagents configured and software programmed to prepare samples in 2 control wells and 10 sample wells-10 test configuration And

		Reagents configured and software programmed to prepare samples in 2 control wells and 4 sample wells-4 test configuration
Instrument Software	Version 1.0	Version 1.3
Instrument Functionality	IVD use only	FLEX configuration allows for IVD or research use of the device system, having different modes separated at log-in without requiring instrument restart

Based on the identical Intended Use of the modified device compared to the marketed Prosigna Breast Cancer Prognostic Gene Signature Assay, and as the fundamental scientific technology of the device has not changed, the modified Prosigna Breast Cancer Prognostic Gene Signature Assay is found to be Substantially Equivalent to the predicate device, the Prosigna Breast Cancer Prognostic Gene Signature Assay cleared under K130010.

References:

Dowsett M. et al. on behalf of the ATAC and LATTE Trialists Group. Comparison of PAM50 Risk of Recurrence Score With Oncotype DX and IHC4 for Predicting Risk of Distant Recurrence After Endocrine Therapy. Journal of Clinical Oncology. ePub ahead of print July 1, 2013 as 10.1200/JCO.2012.46.1558

Gnant M, et al., on behalf of the Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Annals of Oncology 00: 1-7, 2013

Parker J.S., et. al., Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes. Journal of Clinical Oncology, v27 No.8 (2009) 1160-1167